August 22, 2003

Ms. Marianne Horinko
Acting Administrator
U.S. Environmental Protection Agency
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PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

HEADQUARTERS
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Re: Comments on PPG's revised HPV test plan for propanoic acid,2-hydroxy-compound with 3-[2-(dimethylamino)ethyl]1-(2-ethylhexyl)(4-methyl-1,3-phenylene)bis[carbamate](1:1) (referred to below as propanoic carbamate)

Dear Ms. Horinko:

The following are comments on the second revised test plan for propanoic carbamate (CAS no. 68227-46-3), submitted by PPG Industries, Inc., and posted on the EPA's website on July 24, 2003. These comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA), the Physicians Committee for Responsible Medicine (PCRM), the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal and environmental protection organizations have a combined membership of more than ten million Americans.

The first version of the propanoic carbamate test plan, an utterly inadequate document consisting of only a single one-page table, was posted in September 2002. In response to PETA's criticisms, a somewhat improved, although still unsatisfactory, version of PPG's test plan was posted on February 28, 2003, with a 60-day (rather than the usual 120-day) comment period. We then submitted a critique of the revised test plan, focusing mainly on its failure to provide sufficient basic information for a full public review.

PPG's second revised test plan was posted on July 24, 2003. In this test plan the fish toxicity test was, appropriately, omitted, because the log $K_{o/w}$ of propanoic carbamate is above 4.2 (pp. 5-6). However, a combined repeat-dose, reproductive and developmental toxicity test (OECD test guideline 422) is still planned, and this test alone will kill at least 675 animals. An acute toxicity test (OECD test guideline 425) is also planned.

In addition to the second revised test plan, PPG's Dr. James Barter sent PETA the Material Safety Data Sheet (MSDS) for urethane resin on August 7, 2003. This followed an earlier conversation in which Dr. Barter informed PETA that there was, in fact, an MSDS for the substance that is the subject of this test plan. This MSDS has not been posted on the EPA's website. The relationship between urethane resin and propanoic carbamate is unclear, as no CAS number for the former is given in the MSDS. However, Dr. Barter's cover memo states that the urethane resin is a solution of CAS no. 68227-46-3 in a mixed solvent system and is the form in which the material is manufactured and used.

The test plan states that commercial propanoic carbamate product consists of 75% propanoic carbamate, 2-3% methyl isobutyl ketone (CAS no. 108-10-1), 6-7% 2-butoxy ethanol (CAS no. 111-76-2), and 15-17% water. On the other hand, the MSDS states that urethane resin contains 1-5% methyl isobutyl ketone and 10-20% 2-butoxy ethanol, and it does not state the composition of the remaining 75-90% of the resin. It is possible that urethane resin is commercial propanoic carbamate product, and the discrepancy between 2-butoxy ethanol making up 6-7% of the total, as in the test plan, or 10-20%, as in the MSDS, is due to error or re-measurement. However, it is equally possible, judging from the available information, that urethane resin is the resin prepared from the commercial propanoic carbamate product by further reaction (test plan, p. 4). It may also be a different mixture entirely.

Our specific comments on the test plan are as follows:

1. The test plan states that no experimentally determined physicochemical data are available for propanoic carbamate (p. 5), and the urethane resin MSDS provides information only about methyl isobutyl ketone and 2-butoxy ethanol. We cannot understand how PPG can justify planning animal experiments on propanoic carbamate without having fully characterized its physicochemical properties first.

   In an earlier telephone conversation with Dr. Barter, he had informed us that PPG has been using propanoic carbamate since 1990 or earlier. If a company maintains that it has not obtained such basic data as solubility and vapor pressure for a compound to which its employees have been exposed for more than twelve years, this claim must be considered either untrue or indicative of extraordinary negligence.

2. In the case of a compound such as propanoic carbamate, which is aromatic and ionic, with a variety of functional groups (amides, esters, alcohols), a considerable part of any toxicity is likely to be due to metabolites. PPG should therefore predict the principal metabolites from the structure of the compound, and assess the available data before proposing any additional testing on animals.

3. The test plan provides insufficient information about human exposure to propanoic carbamate. It states that 70-85% of the propanoic carbamate manufactured is used as an intermediate (p. 4), but does not state whether it is a closed-system intermediate. It also provides no details about the numbers of workers exposed to propanoic carbamate at the companies to which the other 15-30% is sold. Therefore, even if toxicity data were available, it would be impossible to estimate the human and environmental risks due to propanoic carbamate. One of the most urgent tasks is therefore to carry out an exposure assessment; an epidemiology study would also be appropriate.

4. The characteristics of methyl isobutyl ketone, including toxicity, have been extraordinarily well characterized: our searches of various databases show that more than a thousand toxicity reports have been published. It is toxic (WHO 1990), and according to the urethane resin MSDS, the OSHA-stipulated permissible exposure limit in air is 50 ppm. 2-butoxyethanol is also toxic ("Final report on the safety assessment of butoxyethanol," 1996), and the MSDS states that the OSHA's permissible exposure limit in air is as low as 25 ppm. As these constituents of commercial propanoic carbamate product are toxic, the toxicity of propanoic carbamate will have to be moderately high for it to be of any practical importance; otherwise, the need would be to limit human and environmental exposure to the commercial product, rather than to obtain precise toxicity data on propanoic carbamate. The approximate toxicity of propanoic carbamate can be estimated from analysis of its chemical structure, basic *in vitro* studies, and small-scale epidemiology studies, and we therefore recommend that such investigations should be carried out first. If the results suggest that propanoic carbamate is of low toxicity, a more precise definition of its toxicity will be purely academic and the priority would instead be technical and legislative approaches to further reduction of exposure to the other components of the commercial product.

To conclude, it is premature to plan large-scale tests in the context of the current information vacuum. The data most urgently required at this stage are for exposure and *in vitro* toxicity. Without these basic data, mammalian toxicity data will have little or no value.

Finally, if PPG does wish to carry out the tests indicated in the test plan, there is a range of *in vitro* and *in silico* alternatives to mammalian toxicity tests. We hope PPG will feel free to discuss these with us at its convenience.

Thank you for your attention to these comments. I can be reached at 757-622-7382, ext. 1304, or via e-mail at JessicaS@PETA.org.

Sincerely,

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Federal Agency Liaison

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References

"Final report on the safety assessment of butoxyethanol", *Journal of the American College of Toxicology* 15: 462-526, 1996.

WHO Working Group, "Methyl isobutyl ketone", in *Environmental Health Criteria*, p. 117, 1990.